(Frankland *et al*, 2013). Second, these findings identify a mechanism that could be targeted in memory-related disorders. For example, inefficient neurogenesis-mediated clearance may contribute to human disorders characterized by problems with memory interference (eg, in old age and Alzheimer's disease) or rumination (eg, in PTSD and depression). Interestingly, stress may compound these conditions by further lowering the rates of ongoing neurogenesis.

FUNDING AND DISCLOSURE

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

This project was supported by Canadian Institutes of Health Research (CIHR) grants to PWF (MOP-86762) and SAJ (MOP-74650), and a Brain and Behavior Foundation (NARSAD) to SAJ.

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Neuropsychopharmacology Reviews (2016) **41**, 382–383; doi:10.1038/npp.2015.243

Translational Studies of Sex Differences in Sensitivity to Opioid Addiction

The rapid escalation of opioid addiction, fueled by the increased potency and availability of prescription opioid painkillers, has been declared an epidemic in the US. Although opioid addiction has historically exhibited a substantially higher prevalence in men, adolescent girls are now abusing opioids at a higher rate than boys, the prevalence of fatal opioid overdoses has increased at a higher rate among women relative to men, and women are more likely to use opioids to manage stress. This commentary highlights three examples of recent advancements and ongoing challenges in translational studies of sex differences in sensitivity to the addictive properties of mu opioid receptor (MOR) agonists such as morphine, oxycodone and heroin.

One recent advancement in mechanistic understanding of these sex differences is the finding in *ex vivo* hippocampal slice preparations that a form of MOR-dependent cellular learning is dramatically enhanced in proestrous female rats, when 17-β estradiol levels are at their peak (Harte-Hargrove *et al*, 2015). This female-specific, estradiol-dependent lowering of thresholds for synaptic plasticity may explain, in part, why female rats with high estradiol levels acquire opioid self-administration behavior more rapidly than males (Roth *et al*, 2002). Although these findings mirror the observed 'telescoping' course of illness in women relative to men—characterized by a more rapid progression from initiation of opioid use to an opioid use disorder—there is not direct clinical evidence that estradiol contributes to the telescoping effect.

In a second example, a mouse model of the human MOR A118G SNP replicates many of the phenomena observed in human variants, including reduced morphine analgesia in G allele carriers. But detailed studies of the mouse model also demonstrate that G/G females are significantly less sensitive than A/A females to morphine reward and withdrawal-induced negative affective states, whereas males exhibit similar responses to morphine regardless of allele status (Mague *et al*, 2009). These types of sex by gene interactions, which can have profound effects on addiction risk, are an important future direction in human association studies.

As a final example, recent preclinical findings report that female rats are more sensitive than males to the stress peptide corticotropin releasing factor (CRF) in neural circuits that mediate opioid withdrawal-induced negative affective states (Valentino *et al*, 2013). Specifically, CRF-mediated internalization of CRF type 1 receptors is less efficient in females compared with males such that females have more CRF receptors available for activation in response to stress. Although this type of mechanism could explain why women are more likely than men to use opioids to self-medicate stress and anxiety (McHugh *et al*, 2013), there are no published clinical trials testing the efficacy of CRF antagonists in female opioid addicts.

Substantial sex differences exist across all substances of abuse and in almost every facet of substance use disorders (Greenfield *et al*, 2010). Recent mandates from funding and regulatory organizations (eg, NIH and FDA) requiring researchers to consider both sexes in their studies will certainly advance our understanding of these sex differences. However, translation from preclinical to clinical research often results in an apparent attenuation of effects, as highly controlled studies in simple systems can fail to match clinical findings from complex human samples. As such, it is essential to examine not only main effects of sex on behavioral endpoints, but also potential mechanistic differences that may vary between and within the sexes. Translational approaches designed with the power to identify these complex interactions are the most likely to lead to optimal

therapeutic targets for opioid addiction in both males and females.

FUNDING AND DISCLOSURE

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

This work was supported by National Institutes of Health grant DA035297 (to RKM).

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Neuropsychopharmacology Reviews (2016) **41**, 383–384; doi:10.1038/npp.2015.272

Hormone modulation improves cognition in schizophrenia

Sex and stress hormones are reciprocally regulated and have opposing neurobiological effects (Sinclair *et al*, 2014). Molecular changes in brain sex and stress hormone receptors indicate that these systems are out of balance in people with schizophrenia. Furthermore, increased stress can precipitate the onset or trigger the relapse of psychosis, while low levels of estrogen can exacerbate symptoms in females with schizophrenia (Heringa *et al*, 2015). Also, the sex and stress hormone signaling systems are both activated at a time of increased risk for first developing schizophrenia, during human adolescence, when the prefrontal cortex appears primed to respond to cortisol (Sinclair *et al*, 2011) and when sex steroids are flooding the brain. While we often study these major hormonal systems individually, there is greater awareness that they work in concert and should be considered together.

When the source of peripheral sex steroids are removed, male and female rats will alter their glucocorticoid secretion in response to stress in a gender-specific manner. Thus, one way to modulate the body's reaction to stress is to change sex steroid levels. In addition, high levels of cortisol promote neuronal damage, whereas sex steroids, in particular estrogen, act as neuroprotectants. Males and females have equivalent estrogen receptor (ER) alpha levels in one of the most stress responsive areas of the brain: the human prefrontal cortex (Perlman *et al*, 2005). Thus, stimulation of ER in both males and females may potentially buffer some of the damaging effects of stress.

Historically, the field has approached estrogen as a potential therapy for schizophrenia based on the clinical observation that women can sometimes first manifest the symptoms of schizophrenia later in adult life (>50 years). Because of the known drop in circulating estrogen during female menopause, the obvious strategy was to replace estrogen in these women to test if this could lead to clinical improvement. Most studies suggest that adjunctive estrogens can reduce positive, negative and general symptoms of older women with schizophrenia (Heringa *et al.* 2015). However, long-term estrogen treatment can increase the risk of adverse events. The selective ER modulator raloxifene is an alternative estrogen-based treatment, which has been shown to preserve neural activity and cognition in healthy older men and women. Given that men and women with schizophrenia can express abnormal cerebral cortical ERs (Weickert *et al.*, 2008) and raloxifene could overcome the dominant negative effect of these abnormal receptors on wild-type ER in men and women, we administered raloxifene as an adjunctive treatment to antipsychotics in men and women with schizophrenia to determine the extent to which raloxifene would improve cognitive deficits in schizophrenia. We found that adjunctive raloxifene significantly improved memory and attention and increased hippocampal activity during learning in men and women with schizophrenia (Weickert *et al*, 2015; Kindler *et al*, 2015). Since raloxifene acts as an ER agonist in brain, but can act as an ER antagonist in the periphery, it remains an open question as to how raloxifene may impact stress hormone signaling in schizophrenia.

We do know that estrogen actions are complex. Estrogen can exaggerate stress effects and can augment prefrontal dysfunction during stress in females, but can also protect adolescent females from deleterious effects of social stress (Sinclair *et al*, 2014). In males, testosterone inhibits glucocorticoid secretion. Since raloxifene has potential to increase circulating testosterone levels in men with schizophrenia, it is possible that this increase in testosterone could attenuate the response to stress in men with schizophrenia either directly via testosterone's action on androgen receptor or indirectly on ER via conversion of testosterone to estradiol by aromatase.

FUNDING AND DISCLOSURE

CSW declares no conflict of interest in relation to this work; however, over the past 3 years she has received funds as a consultant for Lundbeck and Roche. TWW declares no conflict of interest in relation to this work; however, over the past three years his wife has received funds as a consultant for Lundbeck and Roche.

ACKNOWLEDGMENTS

This work was supported by the School of Psychiatry of the University of